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Renal complications in COVID-19: A systematic review and meta-analysis

Running Head: Renal manifestations of COVID-19

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ABSTRACT

Purpose: Emerging data suggests coronavirus disease 2019 (COVID-19) has extrapulmonary manifestations but its renal manifestations are not clearly defined. We aimed to evaluate renal complications of COVID-19 and their incidence using a systematic meta-analysis.

Design: Observational studies reporting renal complications in COVID-19 patients were sought from MEDLINE, Embase and the Cochrane Library from 2019 to June 2020. The nine-star Newcastle-Ottawa Scale was used to evaluate methodological quality. Incidence with 95% confidence intervals (CIs) were pooled using random-effects models. **Results:** We included 22 observational cohort studies comprising of 17,391 COVID-19 patients. Quality scores of studies ranged from 4-6. The pooled prevalence of pre-existing chronic kidney disease (CKD) and end-stage kidney disease was 5.2% (2.8-8.1) and 2.3% (1.8-2.8) respectively. The pooled incidence over follow-up of 2-28 days was 12.5% (10.1-15.0) for electrolyte disturbance (eg, hyperkalaemia), 11.0% (7.4-15.1) for acute kidney injury (AKI) and 6.8% (1.0-17.0) for renal replacement therapy (RRT). In subgroup analyses, there was a higher incidence of AKI in US populations and groups with higher prevalence of pre-existing CKD. **Conclusions:** Frequent renal complications reported among hospitalised COVID-19 patients are electrolyte disturbance, AKI and RRT. Aggressive monitoring and management of these renal complications may help in the prediction of favourable outcomes.

Systematic review registration: PROSPERO 2020: CRD42020186873

Keywords renal complications; acute kidney injury; COVID-19; meta-analysis

KEY MESSAGES

- COVID-19 affects multiple organs apart from the respiratory system; however, its renal manifestations are not clearly defined.
- In this systematic meta-analysis of 22 observational cohort studies, the prevalence of pre-existing chronic kidney disease (CKD) in COVID-19 patients was 5.2%.
- The most frequent renal complication was electrolyte disturbance (particularly hyperkalaemia) with an incidence of 12.5% followed by acute kidney injury (AKI) with an incidence of 11.0%; US populations and groups with higher prevalence of CKD had higher incidence of AKI.

Introduction

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) was declared a global public health emergency on 30 January 2020. The COVID-19 pandemic has caused substantial morbidity and mortality worldwide(1) and poses the most significant modern-day public health challenge since the Spanish flu of 1918. Coronavirus disease 2019 predominantly affects the respiratory system, typically manifesting as acute respiratory distress syndrome (ARDS) and severe pneumonia in a few, whereas majority of patients are asymptomatic or present with mild symptoms.(2) The most common symptoms of COVID-19 are fever, cough, myalgia or fatigue.(3) Older patients, males and those with pre-existing comorbidities such as cardiovascular disease (CVD), hypertension, chronic kidney disease, chronic liver disease and diabetes are reported to be more likely to be infected with SARS CoV-2(4) and are at highest risk for severe illness or death.(5, 6) Emerging data suggests that COVID-19 also affects multiple organs, leading to organ failure and eventually death.(7) Common cardiovascular complications reported to be associated with COVID-19 include myocardial injury and heart failure,(8) which have been shown to correlate with the severity of or mortality from COVID-19.(9) Further emerging data also suggests COVID-19 contributes to adverse renal manifestations such as acute kidney injury (AKI), which is also associated with severe COVID-19 or mortality.(10) Given the sparse data, the renal manifestations of COVID-19 are not clearly defined. Despite the rapidly growing knowledge base on the clinical course of the disease, no effective therapeutic agents have been identified. Further data on the clinical course of the disease could help in the development of effective treatment strategies. Understanding the interplay between COVID-19 and its renal manifestations could assist in the management of patients. In this context, we sought to address the following questions using a first systematic meta-analysis of published evidence: (i) what are the renal complications associated with COVID-19? (ii) what is the incidence of these complications? and (iii) are patients with pre-existing renal conditions more susceptible to these renal complications?

Materials and methods

Data sources and search strategy

The review was based on a predefined protocol which was registered in the PROSPERO International prospective register of systematic reviews (CRD42020186873) and it was conducted in accordance with PRISMA and MOOSE guidelines (11, 12) (**Supplementary materials 1-2**). MEDLINE, Embase, and The Cochrane library were searched from 2019 to 13 June 2020 for published studies reporting on renal complications in patients with COVID-19. We combined search terms and key words related to the population (e.g., "COVID-19", "SARS-CoV-2") and outcomes (e.g., "kidney", "renal", "acute kidney injury", "renal transplant therapy", "albuminuria") in humans, which was limited to only reports published in the English language given the potential for duplicate reporting using the same study participants.(13) The detailed search strategy can be found in **Supplementary material 3**. Titles and abstracts were screened for potential eligible studies following retrieval of citations. Following initial screening, full texts of potentially eligible studies were acquired for detailed evaluation. Manual scanning of key articles and review papers was conducted to identify additional articles missed by the search strategy.

Study selection and eligibility criteria

The protocol was pre-specified to include observational studies (prospective and retrospective, nested case-control and case-control designs), non-randomised clinical studies and randomised controlled trials (RCTs) which reported renal complications in patients with COVID-19. Our protocol was pre-specified to include all renal complications anticipated to be reported by studies such as AKI, proteinuria, haematuria, albuminuria, electrolyte disturbance, renal acidosis and alkalosis, need for renal replacement therapy (RRT) and kidney transplant among others. We also sought for studies reporting information on any pre-existing renal conditions (e.g., CKD, end-stage kidney disease); however, they were not included if they did not report on any renal complication. Patients must have had a period of follow-up prior to developing complications.

Data extraction and quality assessment

Using a pre-designed data extraction form, the following data were extracted from the eligible studies: author and year of publication; study characteristics (design, location and date of data collection); patient characteristics (average age, sex, percentage of males, total number of patients, pre-existing renal conditions and their counts and follow-up duration or hospital stay); and renal complications and their counts. Data were extracted and analysed as reported. However, hyperkalaemia was reported by one study and was classified as an electrolyte disturbance to enhance consistency and enable pooling. To minimise over- and under-reporting and maintain consistency, extraction of prevalence and incidence data employed an intention-to-treat principle. Methodological quality of studies was assessed using the nine-star Newcastle-Ottawa Scale (NOS),(14) a tool which has been validated for assessing the quality of non-randomised studies.

Statistical analysis

Pooled prevalence of pre-existing renal conditions (eg, CKD) with 95% confidence intervals (CIs) was calculated from the number of pre-existing renal conditions/total number of patients with COVID-19 in the study. Incidence of renal complications with 95% confidence intervals CIs was estimated from the number of patients experiencing the specific renal complication within period of follow-up (hospital stay)/total number of patients with COVID-19). Given that the data was binary with some low counts, the Freeman-Tukey variance stabilising double arcsine transformation (15) was used in calculating prevalence and incidence estimates as done in previous reports.(16-18) Heterogeneity was assessed and quantified using Cochrane χ^2 and I^2 statistics.(19) We also estimated 95% prediction intervals to determine the degree of heterogeneity, as they provide a region in which about 95% of the true effects of a new study are expected to be found.(20, 21) Pre-defined study-level characteristics such as location, age and comorbidities which may explain heterogeneity were explored using stratified analysis and random effects meta-regression. STATA release MP 16 (StataCorp LP, College Station, TX, USA) was used for all statistical analyses.

Results

Study identification and selection

The process of study selection is presented in **Figure 1**. Overall, a total of 109 articles were identified from the search of major databases and manual scanning of reference lists of relevant articles. After initial screening based on titles and abstracts, full texts of 28 articles were retrieved for further evaluation. Six articles were excluded on the basis of (i) duplicates of the same study (n=4); (ii) outcome not relevant (n=1) and (iii) review article (n=1). This left a total of 22 articles for inclusion in the review.(1, 3, 9, 22-40)

Study characteristics and quality

All 22 studies were based on observational cohort designs (21 retrospective cohorts and 1 prospective cohort), altogether comprising of 17,391 patients with COVID-19 (**Table 1**). Sixteen studies were based in China and six based in the United States. The average age at baseline ranged from 46 to 71 years, with a weighted mean (standard deviation, SD) of 60 (5) years. All studies enrolled both male and female patients. Hospital stay or follow-up duration ranged from 2 to 28 days with a weighted mean (SD) of 7.0 (4.0) days. The overall NOS methodological quality scores of studies ranged from 4 to 6.

Prevalence of pre-existing renal conditions

Across 20 studies providing relevant data, the prevalence of pre-existing CKD in COVID-19 patients ranged from 0.7% to 47.6%, with a pooled random effects prevalence (95% CI) of 5.2% (2.8-8.1; I^2 =98%; 95% CI 97, 98%; *p* for heterogeneity<0.01) (**Figure 2**). The 95% prediction interval for the summary prevalence was 0.0 to 23.1%, suggesting that the true prevalence of pre-existing CKD for any single new study will usually fall within this range. The prevalence of pre-existing end-stage kidney disease based on pooled analysis of two studies was 2.3% (1.8-2.8) (**Figure 2**).

Incidence of renal complications

Over hospital stays ranging from 2 to 28 days following admission, the pooled incidence for AKI (n=22 studies) was 11.0% (7.4-15.1; I^2 =97%; 95% CI 97, 98%; *p* for heterogeneity<0.01) (**Figure 3**). For 14 studies reporting data on the definition of AKI, 12 defined AKI according to Kidney Disease Improving Global Outcomes (KDIGO) criteria (**Appendix 4**).(41) The incidence of electrolyte disturbance (n=2 studies), need

for RRT (n=3 studies) and acidosis (n=2 studies) were 12.5% (10.1-15.0), 6.8% (1.0-17.0) and 5.0 (3.2-7.2) respectively. (**Figure 3**). Based on the report by a single study, the incidence of alkalosis was 6.9 (4.5-10.6).

Given AKI was the outcome commonly reported by studies (22 studies) and with the substantial heterogeneity between contributing studies, we explored for potential sources of heterogeneity using stratified analysis and random effects meta-regression. There was statistically significant evidence of effect modification on the incidence of AKI by location (*p*-value for meta-regression=0.03) and pre-existing CKD (*p*-value for meta-regression<0.001). There was no evidence of effect modification by age (**Figure 4**).

Discussion

In hospitalised patients with renal manifestations of COVID-19, the prevalence of pre-existing CKD was 5.2% and that for end-stage kidney disease was 2.3%. Over hospital stays ranging from 2 to 28 days, AKI was the common outcome reported by studies; however electrolyte disturbance (hyperkalaemia) was the most frequent renal complication with an incidence of 12.5% followed by AKI and RRT at 11.0% and 6.8% respectively. Other reported complications included acidosis and alkalosis. Subgroup analyses suggested evidence of effect modification by location and pre-existing history of CKD on the incidence of AKI; incidence of AKI was higher in the US population (than the Chinese population) and among groups with higher prevalence of pre-existing CKD (than those with lower prevalence). However, AKI incidence was comparable in younger (<60 years) and older (≥60 years) individuals.

Though COVID-19 predominantly affects the respiratory system, there is involvement of multiple organs, such as the gastrointestinal system, the cardiovascular system, the liver as well as the kidneys. These multiple organ disturbances may then interact with each other, which correlates with the severity of the disease. The virus SARS-CoV-2 is known to enter human lung cells by binding to angiotensin-converting enzyme 2 (ACE2).(42) The multiorgan involvement of SARS-CoV-2 has been linked to the wide distribution of ACE2 in the body; the highest expression of ACE2 is found in the ileum and kidneys.(43, 44) In the kidney, ACE2 is expressed on several cells including mesangial cells, podocytes, parietal epithelium of the Bowman's Capsule, and the collecting ducts.(45) Though the mechanisms for the renal manifestations of COVID-19 are still elusive, a complex multifactorial pathway has been proposed and it includes: (i) direct viral involvement and replication in the kidneys leading to dysfunction;(46) (ii) local disruption in renin-

angiotensin-aldosterone system (RAAS) homeostasis;(44) (iii) lung protective fluid management strategy during treatment of ARDS(40) and (iv) as a result of a systemic inflammatory response "cytokine storm".(44)

COVID-19 represents a great medical challenge and appears to have multisystem effects which include renal manifestations. The current data based on up-to-date evidence suggests that AKI is commonly reported as a complication among patients with COVID-19. In addition to pre-existing CKD being associated with severe illness or death in COVID-19,(5) it is also an independent risk factor for AKI.(47) Consistently, our study findings showed that groups with higher prevalence of pre-existing CKD might have higher incidence of AKI. Emerging evidence also suggests that renal manifestations of COVID-19 are also associated with increased risk of severe COVID-19 and fatal outcomes.(10, 30) Monitoring of markers of kidney function during hospitalization for COVID-19 could help in the identification of patients who at high risk for worse outcomes, to enable early and more aggressive intervention. The current evidence provides better insight on the extent of kidney damage by COVID-19. However, more work is needed to help us better understand the pathophysiology underlying renal manifestations of COVID-19, to help in the identification of effective management strategies.

We have provided up-to-date data on the different renal manifestations of COVID-19 as well as their incidence rates. In addition, prevalence estimates of common renal comorbidities have also been presented. Other strengths of this study include ability to synthesise the data quantitatively as well as exploration for sources of heterogeneity. There were some limitations which were mostly inherent and included (i) inability to generalise the findings and the possibility of patient overlap, given that the majority of studies were based in China; (ii) the definition of CKD and classification into stages were not reported by included studies; (iii) a number of studies did not report on the definition for AKI; however, the majority defined AKI according to KDIGO criteria; (iv) studies reporting on the complications of acidosis and alkalosis did not distinguish whether these outcomes were of renal or lung origin; (v) one study reported an outcome of electrolyte disturbance, but did not provide a definition of this; (vi) the potential for differences in the timing during hospitalisation with regards to assessment of complications; and (vii) the low sample sizes of some of the studies.

Conclusion

Aggregate up-to-date synthesis of the existing literature suggests that the most frequent renal complications among patients hospitalised with COVID-19 are electrolyte disturbance (particularly hyperkalaemia), AKI and the need for RRT. Aggressive monitoring and management of these renal complications may help in the prediction of more favourable outcomes.

Disclosure of interest

The authors report no conflicts of interest.

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Figure legends

Figure 1. Selection of studies included in the meta-analysis

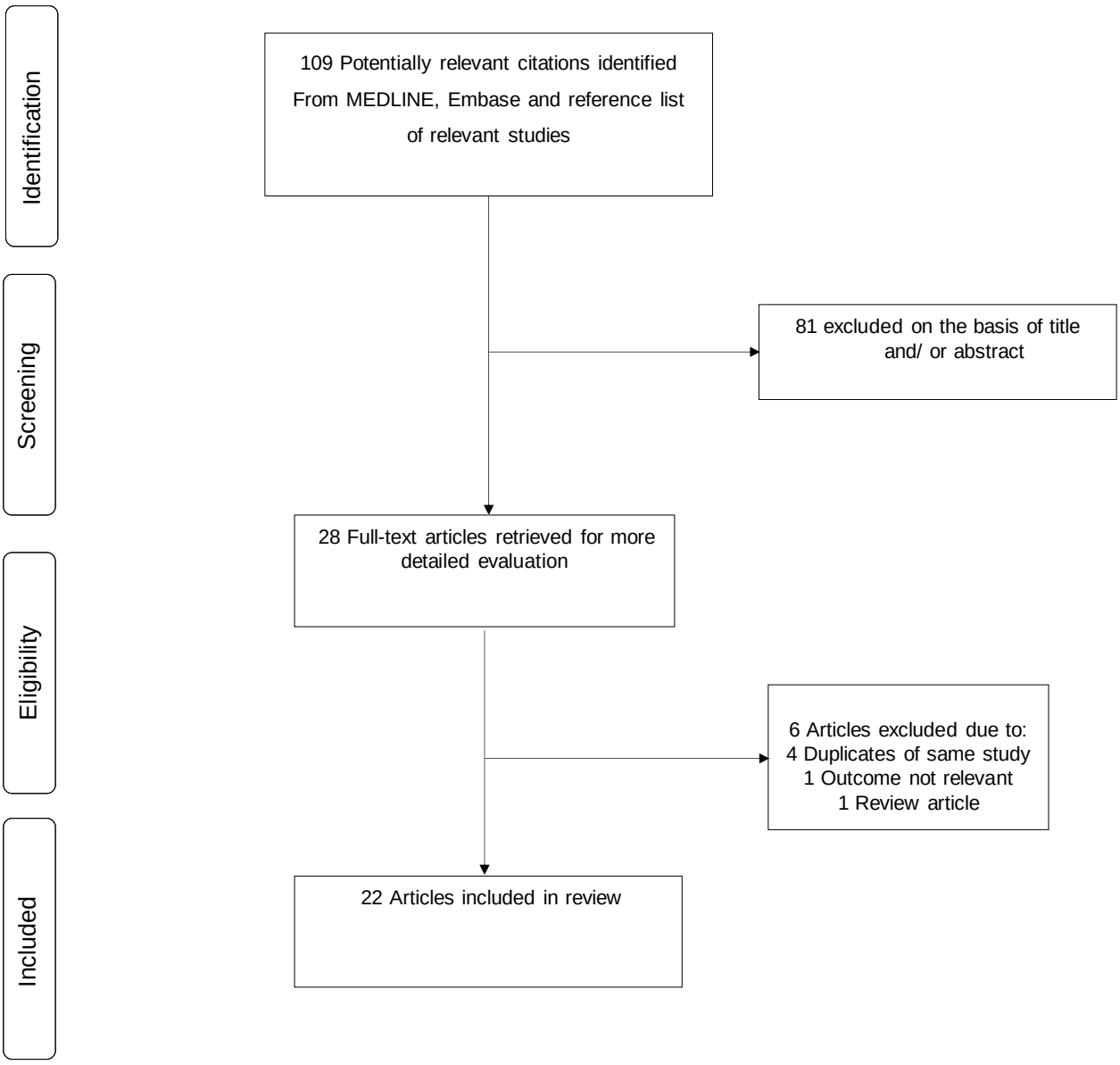
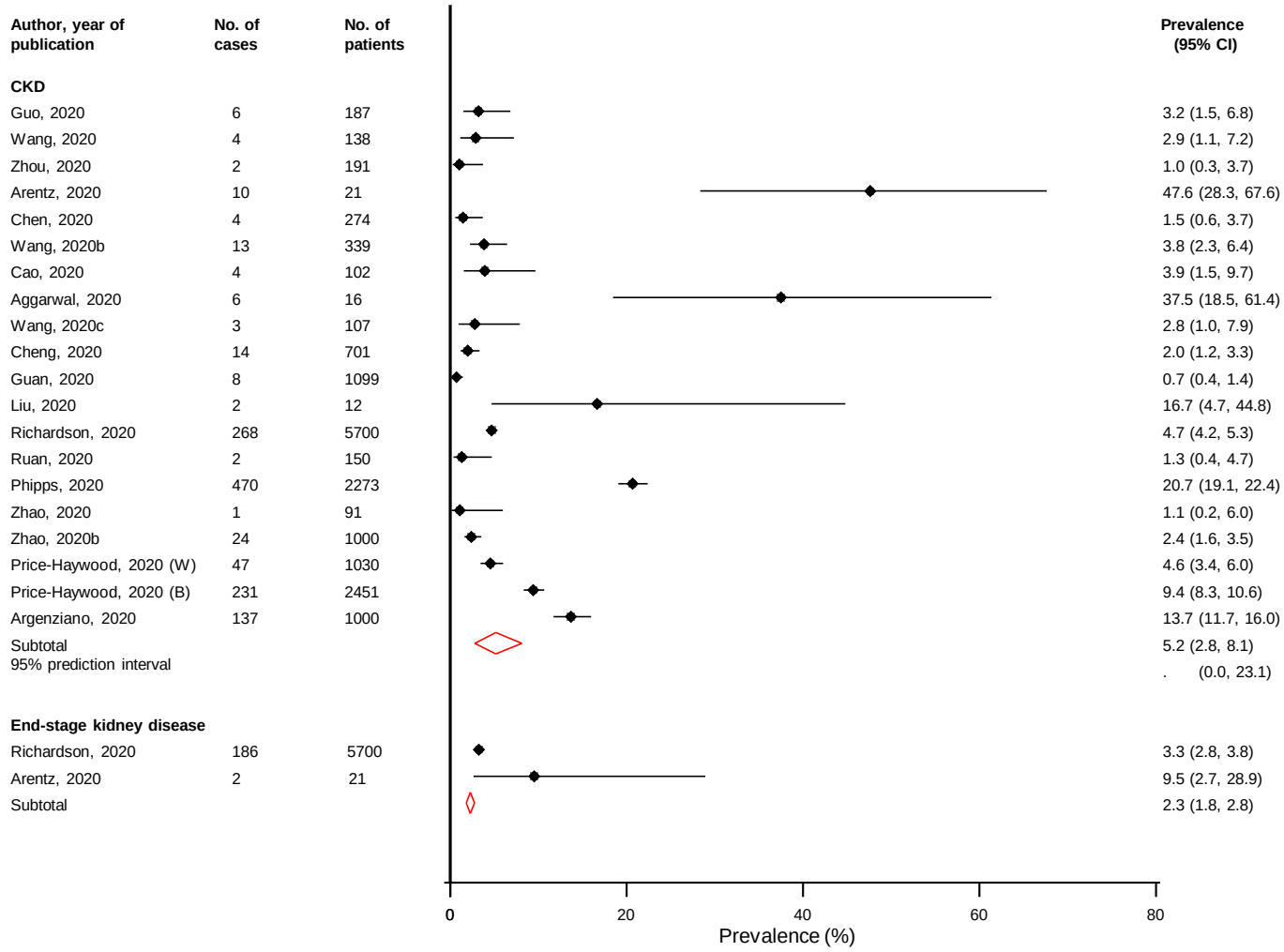
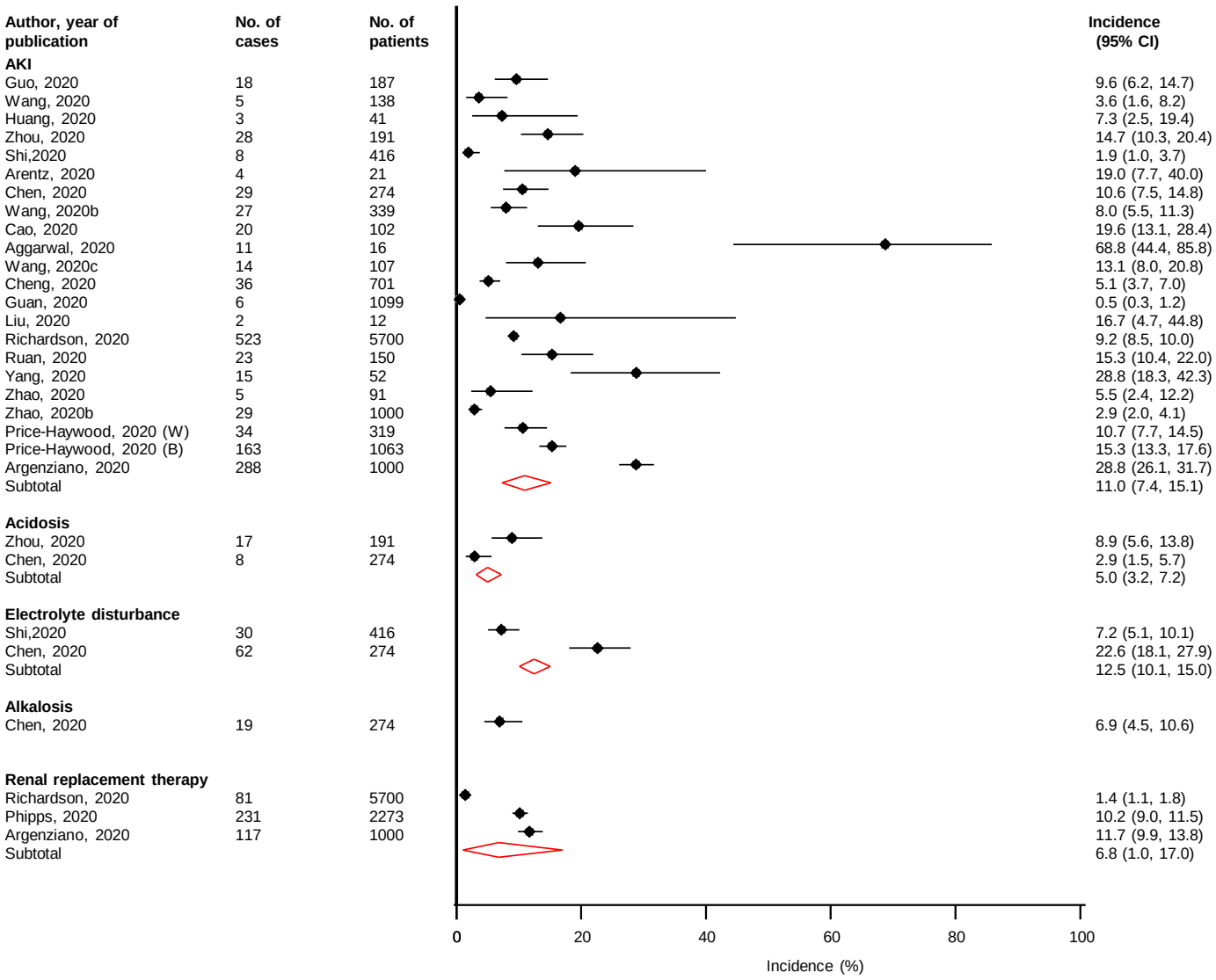


Figure 2. Prevalence of pre-existing renal conditions in COVID-19 patients



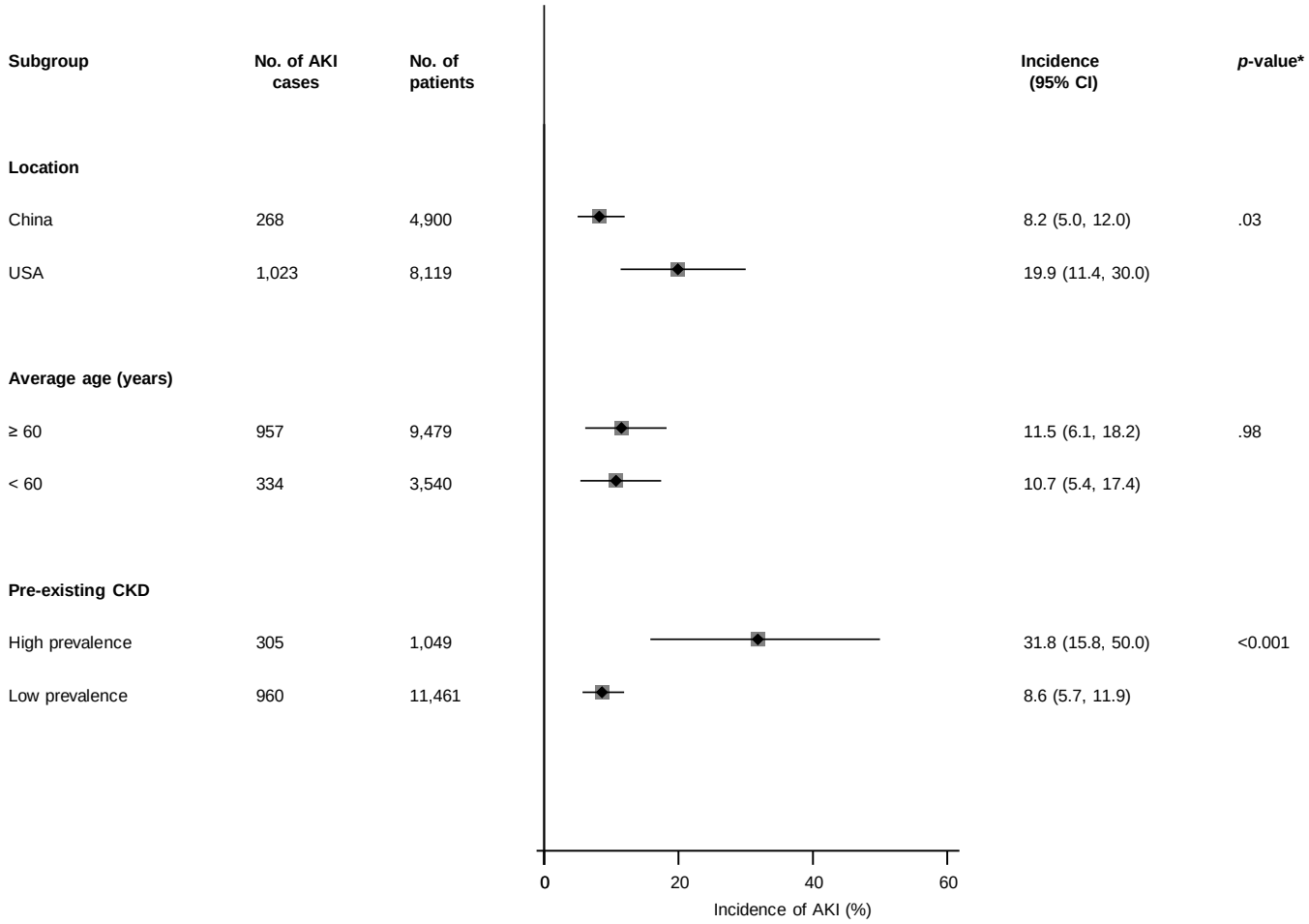
B, black; CI, confidence interval (bars); CKD, chronic kidney disease; W, white

Figure 3. Incidence of renal complications in COVID-19 patients



AKI, acute kidney injury; CI, confidence interval (bars)

Figure 4. Incidence of acute kidney injury in COVID-19 patients, by clinically relevant characteristics



AKI, acute kidney injury; CI, confidence interval (bars); CKD, chronic kidney disease; *, p-value for meta-regression

Table 1. Characteristics of included studies

Author, year of publication	Source of data	Country	Date of data collection	Mean/median age (years)	Males, %	Hospital stay/follow-up (days)	No. of patients	AKI cases	NOS score
Aggarwal, 2020	UnityPoint Clinic	USA	March - April 2020	67.0	75	2.0	16	11	4
Arentz, 2020	Evergreen Hospital in Kirkland, Washington	USA	Feb - March 2020	70.0	52	5.2	21	4	4
Cao, 2020	Zhongnan Hospital of Wuhan University	China	Jan - Feb 2020	54.0	52	11.0	102	20	4
Chen, 2020	Tongji Hospital in Wuhan	China	Jan - Feb 2020	62.0	62	13.0	274	29	4
Cheng, 2020	Tertiary teaching hospital	China	NR	63.0	52.4	10.0	701	36	6
Guan, 2020	National Health Commission	China	Dec - Jan 2020	47.0	58.1	12.0	1099	6	4
Guo, 2020	Seventh Hospital of Wuhan City	China	Jan - Feb 2020	58.5	48.7	16.3	187	18	5
Huang, 2020	Jin Yintan Hospital, Wuhan	China	Dec - Jan 2020	49.0	73	7.0	41	3	4
Liu, 2020	Shenzhen Third People's hospital	China	Dec - Jan 2020	NR	66.7	8.6	12	2	4
Phipps, 2020	New York-Presbyterian network	USA	March – April 2020	65.0	57.0	6.0	2,273	NR	6
Price-Haywood, 2020 (W)	Ochsner Health in Louisiana	USA	March – April 2020	55.5	45.7	7.0	1,030	34	6
Price-Haywood, 2020 (B)	Ochsner Health in Louisiana	USA	March – April 2020	53.6	37.7	6.0	2,451	163	6
Richardson, 2020	12 Hospitals in New York-Northwell Health system	USA	March - April 2020	63.0	60.3	4.5	5700	523	4
Ruan, 2020	Jin Yin-tan Hospital and Tongji Hospital	China	NR	57.7	68	10.1	150	23	4
Shi,2020	Renmin Hospital of Wuhan University	China	Jan - Feb 2020	64.0	49.3	NR	416	8	6
Wang, 2020	Zhongnan Hospital of Wuhan University	China	Jan, 2020	56.0	54.3	7.0	138	5	4
Wang, 2020b	Renmin Hospital of Wuhan University	China	Jan - Feb 2020	71.0	49	28.0	339	27	4
Wang, 2020c	Zhongnan Hospital of Wuhan University and Xishui People's Hospital	China	Up to Feb, 2020	51.0	53.3	11.0	107	14	5
Yang, 2020	Wuhan Jin Yin-tan hospital	China	Dec - Jan 2020	59.7	67	10.0	52	15	4
Zhao, 2020	Jingzhou Central Hospital	China	Jan - Feb 2020	46.0	53.8	NR	91	5	4
Zhao, 2020b	Shouyi and East districts of Renmin Hospital of Wuhan University	China	Jan – Feb 2020	61.0	46.6	7.0	1,000	29	4
Zhou, 2020	Jinyintan Hospital & Wuhan Pulmonary Hospital	China	Dec - Jan 2020	56.0	62	11.0	191	28	5

AKI, acute kidney injury; NOS, Newcastle-Ottawa Scale; NR, not reported

SUPPLEMENTARY MATERIAL

Appendix 1	PRISMA checklist
Appendix 2	MOOSE checklist
Appendix 3	MEDLINE literature search strategy
Appendix 4	Definition of acute kidney injury by eligible studies

Appendix 1: PRISMA checklist

Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	Introduction
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	Methods
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	Methods
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	Methods
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Appendix 3
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	Methods
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	Methods
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	Methods
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	Methods
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	Methods
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	Methods
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	Methods
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	Methods
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	Results, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	Results, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	Results
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	Results, Figures 2-4;
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	Not applicable
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	Not applicable
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	Discussion
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	Discussion
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	Page 10

Appendix 2. MOOSE checklist

Renal complications in COVID-19: A systematic review and meta-analysis

Criteria		Brief description of how the criteria were handled in the review
Reporting of background		
√	Problem definition	Renal manifestations of COVID-19 are not clearly defined.
√	Hypothesis statement	(i) What are the renal complications associated with COVID-19? (ii) What is the incidence of these complications? (iii) Are patients with pre-existing renal morbidities more susceptible to these renal complications?
√	Description of study outcomes	Renal complications
√	Type of exposure	Prevalence and incidence estimates
√	Type of study designs used	Observational cohort designs and clinical studies
√	Study population	Adult patients with COVID-19
Reporting of search strategy should include		
√	Qualifications of searchers	Setor K. Kunutsor, PhD
√	Search strategy, including time period included in the synthesis and keywords	Time period: from inception to 14 June 2020 The detailed search strategy can be found in Appendix 3
√	Databases and registries searched	MEDLINE, Embase and The Cochrane Library
√	Search software used, name and version, including special features	OvidSP was used to search Embase and MEDLINE EndNote X9 used to manage references
√	Use of hand searching	We searched bibliographies of retrieved papers
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart. The citation list for excluded studies are available on request.
√	Method of addressing articles published in languages other than English	Not applicable
√	Method of handling abstracts and unpublished studies	Not applicable
√	Description of any contact with authors	None
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria are described in the Methods section.
√	Rationale for the selection and coding of data	Data extracted from each of the studies were relevant to the population characteristics, study design, exposure, and outcome.
√	Assessment of confounding	We assessed confounding by ranking individual studies on the basis of different adjustment levels and performed sub-group analyses to evaluate differences in the overall estimates according to levels of adjustment.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Study quality was assessed based on the nine-star Newcastle–Ottawa Scale using pre-defined criteria namely: population representativeness, comparability (adjustment of confounders), ascertainment of outcome. Sensitivity analyses by several quality indicators such as study size, duration of follow-up, and adjustment factors.
√	Assessment of heterogeneity	Results
√	Description of statistical methods in sufficient detail to be replicated	Described in methods section
√	Provision of appropriate tables and graphics	Table 1; Figures 1-4
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Figure 2-4
√	Table giving descriptive information for each study included	Table 1
√	Results of sensitivity testing	Not applicable
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates
Reporting of discussion should include		
√	Quantitative assessment of bias	The systematic review is limited in scope, as it involves studies with limited information.

√	Justification for exclusion	All studies were excluded based on the pre-defined inclusion criteria in methods section.
√	Assessment of quality of included studies	Brief discussion included in 'Methods' section
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	Discussion
√	Generalization of the conclusions	Discussed in the context of the results.
√	Guidelines for future research	We recommend large-scale studies when more data becomes available
√	Disclosure of funding source	In "Acknowledgement" section

Appendix 3: MEDLINE literature search strategy

1 exp Acute Kidney Injury/ (45784)
2 exp Renal Insufficiency/ (171007)
3 exp Proteinuria/ (38920)
4 exp Hematuria/ (11861)
5 exp Albuminuria/ (14899)
6 kidney replacement.mp. (227)
7 exp Kidney Transplantation/ (94773)
8 electrolyte imbalance.mp. (6681)
9 exp Acidosis/ (31908)
10 exp Alkalosis/ (4723)
11 exp Hyperkalemia/ (5857)
12 COVID-19.mp. (5083)
13 SARS-CoV-2.mp. (1378)
14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (331623)
15 12 or 13 (5233)
16 14 and 15 (18)
17 limit 16 to (english language and humans and yr="2019 -Current") (11)

Each part was specifically translated for searching alternative databases.

Updated MEDLINE literature search strategy

1 COVID-19.mp. (9980)
2 SARS-CoV-2.mp. (3014)
3 exp Kidney/ (348489)
4 renal.mp. (674103)
5 1 or 2 (10295)
6 3 or 4 (846324)
7 5 and 6 (111)
8 limit 7 to (english language and humans and yr="2020 -Current") (61)

Appendix 4: Definition of acute kidney injury by eligible studies

Author, year of publication	AKI definition
Argenziano, 2020	Definition not specified
Aggarwal, 2020	NR
Arentz, 2020	Defined by criteria from KDIGO and the International Society of Nephrology
Cao, 2020	NR
Chen, 2020	Identified on the basis of the highest serum creatinine level according to the KDIGO criteria
Cheng, 2020	Increase in serum creatinine by 0.3 mg/dl within 48 hours or a 50% increase in serum creatinine from baseline within 7 days according to the KDIGO criteria
Guan, 2020	Based on the highest serum creatinine level and urine output according to the KDIGO criteria
Guo, 2020	NR
Huang, 2020	Identified on the basis of the highest serum creatinine level or urine output according to the KDIGO criteria
Liu, 2020	NR
Phipps, 2020	NR
Price-Haywood, 2020	NR
Richardson, 2020	Increase in serum creatinine by 0.3 mg/Dl or more (≥26.5 μmol/L) within 48 hours or an increase in serum creatinine to 1.5 times or more baseline within the prior 7 days compared with the preceding 1 year of data in acute care medical records according to KDIGO criteria
Ruan, 2020	NR
Shi,2020	Defined according to KDIGO criteria
Wang, 2020	Defined according to KDIGO criteria
Wang, 2020b	Defined according to KDIGO criteria
Wang, 2020c	Defined according to KDIGO criteria
Yang, 2020	Identified on the basis of serum creatinine according to KDIGO criteria
Zhao, 2020	Identified according to elevated creatinine and uric acid levels
Zhao, 2020b	Highest serum creatinine level increased by more than 26.5 μmol/L (0.3 mg/dL) within 48 hours; serum creatinine exceeded the baseline value by 1.5-fold (confirmed or estimated to occur within 7 days); urine output <0.5 ml/kg * h), lasting more than 6 hours.
Zhou, 2020	Defined according to KDIGO criteria

AKI, acute kidney injury; KDIGO, Kidney Disease Improving Global Outcomes; NR, not reported